A Three-arm Randomized Clinical Trial Comparing Continuous Femoral Plus Single-injection Sciatic Peripheral Nerve Blocks *versus* Periarticular Injection with Ropivacaine or Liposomal Bupivacaine for Patients Undergoing Total Knee Arthroplasty

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ABSTRACT

Background: Multimodal analgesia is standard practice for total knee arthroplasty; however, the role of regional techniques in improved perioperative outcomes remains unknown. The authors hypothesized that peripheral nerve blockade would result in lower pain scores and opioid consumption than two competing periarticular injection solutions.

Methods: This three-arm, nonblinded trial randomized 165 adults undergoing unilateral primary total knee arthroplasty to receive (1) femoral catheter plus sciatic nerve blocks, (2) ropivacaine-based periarticular injection, or (3) liposomal bupivacaine-based periarticular injection. Primary outcome was maximal pain during postoperative day 1 (0 to 10, numerical pain rating scale) in intention-to-treat analysis. Additional outcomes included pain scores and opioid consumption for postoperative days 0 to 2 and 3 months.

Results: One hundred fifty-seven study patients received peripheral nerve block (n = 50), ropivacaine (n = 55), or liposomal bupivacaine (n = 52) and reported median maximal pain scores on postoperative day 1 of 3, 4, and 4.5 and on postoperative day 0 of 1, 4, and 5, respectively (average pain scores for postoperative day 0: 0.6, 1.7, and 2.4 and postoperative day 1: 2.5, 3.5, and 3.7). Postoperative day 1 median maximal pain scores were significantly lower for peripheral nerve blockade compared to liposomal bupivacaine-based periarticular injection ($P = 0.016$; Hodges–Lehmann median difference [95% CI] = −1 [−2 to 0]). After postanesthesia care unit discharge, postoperative day 0 median maximal and average pain scores were significantly lower for peripheral nerve block compared to both periarticular injections (ropivacaine: maximal −2 [−3 to −1]; $P < 0.001$; average −0.8 [−1.3 to −0.2]; $P = 0.003$; and liposomal bupivacaine: maximal −3 [−4 to −2]; $P < 0.001$; average −1.4 [−2.0 to −0.8]; $P < 0.001$).

Conclusions: Ropivacaine-based periarticular injections provide pain control comparable on postoperative days 1 and 2 to a femoral catheter and single-injection sciatic nerve block. This study did not demonstrate an advantage of liposomal bupivacaine over ropivacaine in periarticular injections for total knee arthroplasty. **(Anesthesiology 2017; XXX:00-00)**

CLINICAL pathways incorporating multimodal analgesic regimens including regional anesthetic techniques are widely used for patients undergoing total knee arthroplasty.[1–5] Oral analgesics, local anesthetic adjuvants, peripheral nerve blockade, and periarticular injection (also known as local infiltration analgesia) are a few of the commonly employed modalities.[6,7] When incorporated into a comprehensive clinical pathway, these pain management techniques have been shown to improve perioperative outcomes including improved patient comfort, a reduction in hospital length of stay, enhanced patient satisfaction, and an earlier return to work and recreational activities.[2,8] However, the optimal components of this multimodal approach and the role of regional techniques in improved perioperative outcomes remain unknown.

What We Already Know about This Topic

- Multimodal analgesia provides very good pain relief for patients after total knee arthroplasty
- Peripheral nerve blocks and periarticular injections of local anesthetic are commonly used components of multimodal analgesic strategies

What This Article Tells Us That Is New

- In a three-arm randomized trial involving 165 adult knee arthroplasty patients, femoral and sciatic nerve blocks, ropivacaine-based periarticular injection, and liposomal bupivacaine-based periarticular injection all provided good analgesia
- The peripheral nerve block strategy provided some advantages in terms of pain relief and opioid sparing at early time points after surgery

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Advanced pain management techniques are associated with a unique set of risks and benefits. For example, although a femoral and sciatic nerve block would provide complete postoperative analgesia after a total knee arthroplasty, these techniques may be associated with perioperative nerve injury, prolonged dysesthesias, motor weakness, nerve catheter dislodgement, or bleeding and infectious complications.[9,10] In contrast, the use of periarticular infiltration may minimize concerns related to nerve injury, dysesthesias, and motor weakness but at the potential expense of inferior analgesia when compared to peripheral nerve blockade.[6,7,11]

Due to the quadriceps weakness associated with femoral nerve blockade and alternative pain management techniques preserving motor function,[12–15] several alternative analgesic practices, including adductor canal block,[16] saphenous nerve block,[17] selective tibial nerve block,[18] as well as periarticular injection techniques,[19] have been introduced into modern clinical pathways. Further adding to the vast amount of variation in practice, a new formulation of local anesthetic, liposomal bupivacaine, is now widely available and is approved for wound infiltration.[20,21] This liposomal formulation has been detected in serum samples beyond 72 h[22] but has not yet been demonstrated to be clinically superior to nonencapsulated forms of local anesthetic for periarticular injections.[21]

Prospective clinical trials comparing these analgesic modalities to one another are lacking, resulting in a significant knowledge gap and inability to determine which pain management technique is best suited for patients undergoing primary total knee arthroplasty. Therefore, the goal of the current study was to compare pain control and long-term pain outcomes between a combination of peripheral nerve blocks (femoral nerve catheter and single-injection sciatic nerve block) and two different solutions for periarticular injections (ropivacaine-based or liposomal bupivacaine-based local anesthetic solutions). We hypothesized that when incorporated into a comprehensive multimodal analgesic pathway for patients undergoing total knee arthroplasty, peripheral nerve blockade including continuous femoral nerve plus single-injection sciatic nerve blockade would result in lower postoperative pain scores and lower consumption of opioid medications compared to periarticular injections using ropivacaine- or liposomal bupivacaine-based solutions.

Materials and Methods

Study Design and Patient Enrollment

This study was approved by the Institutional Review Board (14-002083) of Mayo Clinic, Rochester, Minnesota; written informed consent was obtained from all subjects, and the study was posted on clinicaltrials.gov (NCT02223364, July 29, 2014) before patient enrollment. The full protocol of the study is available upon request. We conducted a three-arm, parallel, outcome adjudicator-blinded, superiority, randomized-controlled clinical trial in adult patients undergoing elective, unilateral primary total knee arthroplasty from October 2014 to December 2015 at a single site. This study manuscript was compiled in accordance with the Consolidated Standards of Reporting Trials guidelines.[23,24]

All consecutive American Society of Anesthesiologists (ASA) physical classification I to III (older than or equal to 18 yr) patients undergoing an elective, unilateral primary total knee arthroplasty were assessed for eligibility by trained study coordinators, and those meeting inclusion and exclusion criteria were randomized to one of three interventions (fig. 1): (1) continuous femoral nerve catheter plus single-injection proximal sciatic nerve block; (2) periarticular injection with ropivacaine mixture; or (3) periarticular injection with liposomal bupivacaine mixture. We excluded patients with documented chronic pain syndromes, history of long-term use of daily opioids (more than 1 month) with oral morphine equivalent of greater than 5 mg/day, body mass index greater than 40 kg/m^2, allergies to study medications, impaired cognitive function, contraindication to regional anesthesia, major systemic illnesses such as severe renal (estimated glomerular filtration rate less than 50 ml/min), cardiac (congestive heart failure New York Heart Association class III to IV), or severe hepatic disorder defined as current or past diagnosis of acute/subacute liver necrosis, acute hepatic failure, chronic liver disease, liver abscess, hepatic coma, hepatorenal syndrome, and other disorders of the liver. After enrollment of 40 study participants, to increase enrollment numbers, the authors of this study requested and received institutional review board's approval to modify the protocol to (1) allow short-term acute use of daily opioids (oral morphine equivalents less than or equal to 30 mg/day for less than 1 month) and (2) increase the body mass index threshold from greater than 40 to greater than 45 kg/m^2 to better reflect our patient population. Potential study participants were identified from individual surgeons' registration lists in advance of the surgical date. During the preoperative clinic visit, a study coordinator interviewed eligible patients, completed the informed consent, and enrolled the patient for study participation. Upon enrollment, study patients were assigned the available study number. A randomization schedule that documented the randomized treatment allocation for each study number was used by our Anesthesia Clinical Research Unit to assign each patient to a study arm. The computer-generated randomization schedule was prepared by our statistician using blocks of six to ensure that after every sixth patient was enrolled, an equal number of patients would be assigned to each treatment group. The randomization was concealed from the investigators through central randomization. To avoid loss of concealment, the group to which the patient was allocated could only be accessed after registration for surgery. Patients, healthcare providers, or data collectors were not masked to group allocation. However, outcome adjudicators were blinded to the prospectively collected data.

Anesthetic and Surgical Technique

Following the Multimodal Analgesia Total Joint Pathway (fig. 2), all study patients were provided a combination of

Total Knee Arthroplasty Intervention Group

Peripheal Nerve Block Group (PNB)	*Local Anesthetic Bolus*	*Total Volume of Preoperative Bolus*	*Adjuvants in Preoperative Bolus*	*Local Anesthetic Infusion*
Femoral Nerve Catheter	Bupivacaine 0.5% (preoperative) Bupivacaine 0.2% (upon PACU arrival)	20 mL	1:200,000 Epinephrine	Bupivacaine 0.2% at 10 ml/hr initiated in PACU until 05:00 day after surgery; then 0.1% at 10 ml/hr until removal at 06:00 second day after surgery
Single-Injection Sciatic Nerve	Bupivacaine 0.25%	30 mL	100 mcg Clonidine 1:400,000 Epinephrine	N/A
Ropivacaine Group (PAI-R)	***50-74.9kg***	***75-99.9 kg***	***100-125kg***	***Total Volume of Solution***
Ropivacaine	200 mg	300 mg	400 mg	120 mL*
Epinephrine	100 mcg	200 mcg	300 mcg	
Ketorolac	30 mg	30 mg	30 mg	
Liposomal Bupivacaine Group (PAI-L)	***50-125kg***			***Total Volume of Solution***
Liposomal Bupivacaine	266mg			120 mL*
Ketorolac	30mg			
Bupivacaine	125mg			
Epinephrine	125mcg			

Fig. 1. Total knee arthroplasty intervention group. *Diluted with saline to make a total volume of 120 ml. PACU = postanesthesia care unit; PAI-L = periarticular injection liposomal bupivacaine; PAI-R = periarticular injection ropivacaine; PNB = peripheral nerve block.

oral analgesic medications preoperatively regardless of group allocation consisting of immediate or controlled-release oxycodone, celecoxib, and acetaminophen, unless contraindicated. Intraoperative management included the primary anesthesia type, intraoperative monitoring (other than standard ASA monitoring), and supplemental analgesia, and antiemetic medications were administered at the discretion of the attending anesthesiologist. A spinal anesthetic was recommended, but not required, and did not contain an opioid medication. Unless contraindicated, all patients received 4 mg intravenous dexamethasone intraoperatively. All patients received a posterior stabilized total knee arthroplasty through a medial parapatellar approach, and all procedures were performed by high-volume, lower-extremity arthroplasty surgeons at the Mayo Clinic Hospital, Methodist Campus in Rochester, Minnesota.

Peripheral Nerve Block Group

All peripheral nerve blocks were placed before induction of anesthesia. After intravenous access was obtained, patients were monitored and sedated with intravenous midazolam (1 to 4 mg) and fentanyl (50 to 200 μg). Regional blocks were placed by either anesthesiologists with significant regional anesthesia experience or resident/fellow trainees under direct supervision of regional anesthesia experts.

The ultrasound-guided femoral nerve block was placed with the patient in the supine position. After sterile skin preparation with chlorhexidine and then draping, a linear probe with a frequency ranging from 13–6 MHz ultrasound transducer (M-Turbo® or X-Porte®, SonoSite Inc., USA) was placed on the inguinal crease. The femoral nerve was sonographically identified lateral to the femoral artery. The skin was infiltrated with 1% lidocaine, and an in-plane (lateral to medial) or out-of-plane (caudal to cranial) short-axis needle approach to the femoral nerve occurred with an 18-gauge 2- or 4-inch Contiplex® Tuohy (B. Braun, USA) nonstimulating catheter system. A peripheral nerve stimulator was used in addition to ultrasound guidance at the discretion of the anesthesiologist. The catheter was placed adjacent to the nerve, and local anesthetic spread was visualized using ultrasound guidance around the femoral nerve. The sciatic nerve block was placed using nerve stimulation *via* the classic posterior or subgluteal approach.[25] The local anesthetic solutions used for each block are displayed in figure 1. A

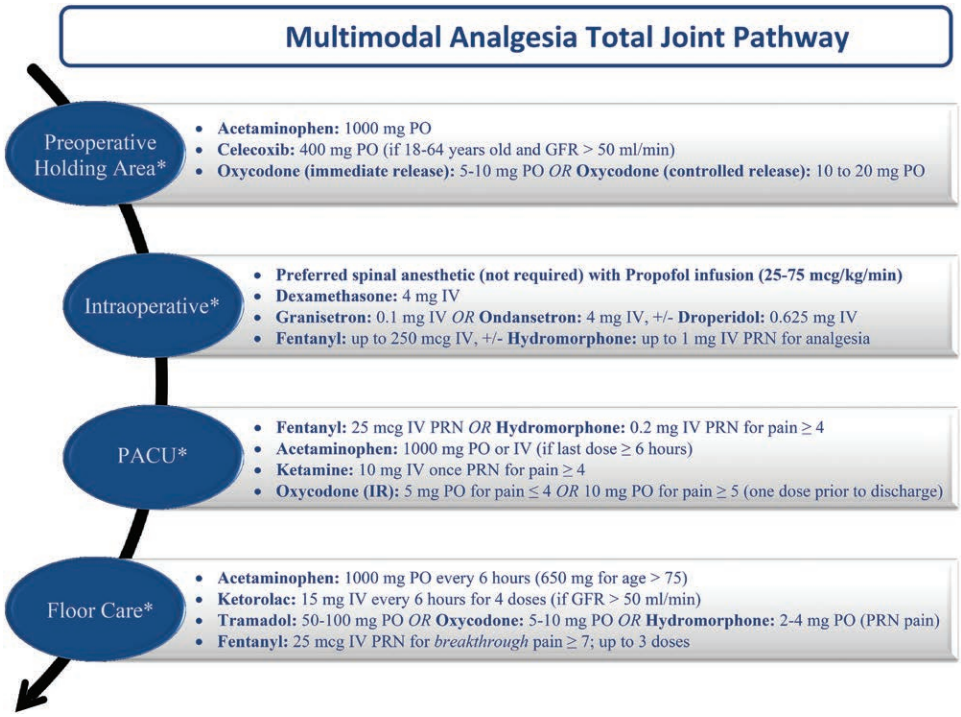

Fig. 2. Multimodal analgesia total joint pathway. *Preoperative holding area, intraoperative, and postanesthesia care unit (PACU) medication administration is at the discretion of the anesthesiologist. Floor care medication administration is at the discretion of the orthopedic surgical team. The medications listed are the recommended analgesic options for each patient. All pain scores listed refer to the numeric rating scale (0 to 10). GFR = glomerular filtration rate; IR = immediate release; IV, intravenous; PO = per os; PRN = pro re nata (as necessary).

10-ml bolus of 0.2% bupivacaine was administered to the femoral nerve catheter again in the postanesthesia care unit (PACU), and an infusion of 0.2% bupivacaine at 10 ml/h was initiated. At 5:00 AM the day after surgery, the infusion was changed to 0.1% bupivacaine at 10 ml/h. This infusion was continued until postoperative day (POD) 2 when the infusion and catheter were discontinued at or slightly before 6:00 AM. Quadriceps motor strength (0 = absent or diminished; 1 = at baseline) and sensory exam (0 = sensation to pinprick of anterior thigh diminished or absent; 1 = sensation to pinprick of anterior thigh normal) and foot dorsiflexion motor strength (0 = absent or diminished; 1 = at baseline) and sensory exam (0 = sensation to pinprick of the plantar surface was absent or diminished; 1 = sensation to pinprick of the plantar surface at baseline) were assessed preoperatively (at least 30 min after the placement of the block), if time permitted, postoperatively in the recovery room, or on the hospital ward the day of surgery after the spinal anesthetic had regressed sufficiently. A successful block was defined as having a rating of 0 in either sensory or motor exam for both the femoral and sciatic nerve distribution.

Ropivacaine and Liposomal Bupivacaine Periarticular Injection Groups

Patients in the periarticular injection groups received either a weight-based periarticular injection solution with ropivacaine or a standardized-dose periarticular injection solution with liposomal bupivacaine by our surgical colleagues (fig. 1). The method of periarticular injection for patients in the ropivacaine and liposomal bupivacaine groups was performed in a consistent manner. Before cementation, the posterior capsule was injected with approximately 30-ml injectate solution through multiple capsular punctures beginning medial to the midline of the posterior capsule and proceeding further medially. This method minimizes the risk of postoperative peroneal nerve dysfunction with injection of the solution into the posterolateral capsule.[26] Of note, aspiration was completed before injecting the posterior capsule to minimize the likelihood that the needle was in the popliteal vessels.[26] The synovium overlying the distal femur medially, laterally, and in the suprapatellar pouch was injected with approximately 30 ml, and then 30 ml was injected in a systematic fashion into the arthrotomy including the medial and lateral retinaculum.[19,27] The final 30-ml injectate solution was injected into the subcutaneous tissue.[27]

Postoperative Management

Postoperatively, all participants were transferred to the PACU and were managed similarly regardless of group allocation. Patient requests for additional analgesics were at the discretion of the anesthesiologist in the PACU. Oral and/or intravenous analgesics on the ward and after discharge were at the discretion of the orthopedic surgical service (fig. 2). The peripheral nerve catheters were managed by the acute

pain service, which provides 24-h in-hospital coverage with daily morning rounds.

Primary and Secondary Outcomes

The primary outcome was median maximal pain score during the first postoperative morning 6:00 AM to 12:00 PM measured on a 0 to 10 numeric pain rating scale (NRS) by orthopedic nursing personnel. Additional NRS pain scores were measured in the recovery room and then per orthopedic floor nursing protocol that includes an assessment within 1 h of patient arrival and then every 4 h. Additional pain assessments occur 1 h after oral pain medicine was administered or within 5 min if intravenous pain medicine was given. Pain scores were collected for a minimum of 48 h and a maximum of 96 h from the time of the initial assessment in the recovery room unless the patient was discharged from the hospital. All pain assessments were collected based on routine clinical documentation by each speciality.

Additional outcome measures included opioid consumption during hospitalization in daily oral morphine equivalents documented by either anesthesia or the orthopedic nursing staff, balance testing using unipedal stance time preoperatively and by phone interview 12 to 16 weeks from the date of surgery, length of hospital stay, and chronic pain assessments reported at 12 to 16 weeks. Complications or adverse events such as patient falls, nerve injury, surgical infection, or unanticipated intensive care unit admission were also noted. To measure clinical balance, unipedal stance time was collected by our trained study coordinators within 1 week preoperatively and by phone interview 12 to 16 weeks from the date of surgery. Timing for unipedal stance time (in seconds) began upon withdrawal of support and continued until the uplifted foot returned to the floor, the patient required support, or the patient reached a time limit of 30 s (maximum 30 s).[28] The best performance of three repetitions was recorded for each limb.

Health-related quality of life was collected by our study coordinators using the Medical Outcomes Study 36-Item Short-Form questionnaire including assessments for physical functioning, role functioning-physical, bodily pain, general health, energy, social functioning, role functioning-emotional, and mental health.[29] Patients were instructed on the 36-Item Short-Form by study coordinators during the preoperative visit, and information was collected both preoperatively and postoperatively by phone interview 12 to 16 weeks from the date of surgery. For patients reporting surgery-related pain greater than 3 on the NRS at the 3-month postoperative visit, a Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)[30] was completed by study coordinators.

Sample Size/Statistical Power Considerations

The sample size for this three-arm trial was determined for the primary endpoint of maximal pain during the first postoperative morning measured using a 0 to 10 NRS pain scale. For this endpoint, a pain score difference between groups of 2 or larger was considered clinically relevant, and to control for multiple comparisons, we specified *a priori* that pairwise comparisons would be performed with $P < 0.017$ (*i.e.*, Bonferroni corrections) used to denote statistical significance. Based on the data from our own clinical practice and the retrospective study by Perlas *et al.*,[31] the primary endpoint SD was assumed to be approximately 3.0. Under this assumption, we determined that a sample size of n = 50 per group would provide statistical power (two-tailed, $\alpha = 0.017$) of approximately 80% to detect a clinically relevant difference between groups for the primary endpoint. For the secondary outcome of opioid requirements, sample size estimates were also considered. Spangehl *et al.*[19] reported in total knee arthroplasty patients mean ± SD morphine equivalents on day 1 of 43 ± 29 mg for peripheral nerve blockade and 49 ± 29 mg for periarticular injection. Under the assumption that the SD is 30 mg, a sample size of n = 50 per group would also provide statistical power (two-tailed, $\alpha = 0.017$) of 80% to detect a difference between groups of 20 mg. To account for up to 10% attrition due to canceled surgery or late patient ineligibility reasons, a sample size of n = 165 (55 per group) was selected.

Data Analysis

Data are presented using mean ± SD or median (25th, 75th percentiles) for continuous variables and frequency counts and percentages for nominal variables. For the primary endpoint of maximal pain during the first postoperative morning and secondary endpoints including average and maximal NRS pain scores and opioid requirements through POD 2, pairwise treatment group comparisons were performed using the rank sum test. For these outcomes, two-tailed $P < 0.017$ was considered statistically significant. To supplement the results of the rank sum test, the point estimate and 95% CI for Hodges–Lehmann median difference is presented for each of the pairwise comparisons. Other hospital outcomes were compared across all three groups; the Kruskal–Wallis test was used for hospital length of stay and Fisher exact test for adverse events and the use of rescue IV opioids. The mental and physical composite scores from the 36-Item Short-Form were calculated at baseline and 3 months. For these endpoints, within the group allocation, differences (baseline *vs.* 3 months) were assessed using the paired *t* test, while comparing between the allocated groups, differences were assessed using ANOVA. Since data for the unipedal stance time are censored at 30 s, data from baseline and 3 months were compared using proportional hazards regression with subject included as a random effect to take into account the repeated measurements within subjects. Other outcomes collected at 3 months were compared across groups using the Kruskal–Wallis test for continuous variables and Fisher exact test for nominal variables. Due to larger than expected baseline imbalance across groups, *post hoc* analyses were performed for the primary endpoint of maximal pain during

the first postoperative morning to assess differences between treatment group after adjusting for sex, ASA status, and type of anesthesia. The analyses were performed using linear regression with treatment group as the explanatory variable of interest and sex (male *vs.* female), ASA status (I/II *vs.* III), and type of anesthesia (general *vs.* regional) included as covariates. For these models, quantile—quantile plots of the residuals were reviewed to assess normality. In all cases, two-tailed *P* values are reported with no adjustments for multiple comparisons. Analyses were performed using SAS version 9.3 (SAS Institute Inc, USA).

Results

Between November 2014 and December 2015, 165 patients undergoing elective, unilateral primary total knee arthroplasty were randomized to one of the three interventions (n = 55 each). Figure 3 shows the study flow following Consolidated Standards of Reporting Trials guidelines.[22,23] Of the 165 patients randomized, two blocks failed in the peripheral nerve block group, and 9 patients did not receive the allocated treatment. A blinded three-person adjudication committee, unaware of treatment or outcome, was formed to evaluate why the nine cases did not receive their allocated treatment and determine whether the patient should have been enrolled based on inclusion and exclusion criteria.[32] A majority decision between the three committee members determined that eight of the patients were incorrectly enrolled because of an unanticipated change in their exclusion criteria (fig. 3). The committee found that one patient should be included in data analysis for intention to treat. After randomization, this patient's original surgery date was rescheduled, which resulted in missed enrollment, with another surgeon not involved in the study. Of note, the patient received similar techniques for his multimodal analgesic management. Therefore, the final study sample includes 157 patients (50 patients in the peripheral nerve block group, 55 in the ropivacaine periarticular injection group, and 52 in the liposomal bupivacaine periarticular injection group). Baseline patient characteristics are presented in table 1.

Postoperative pain scores are summarized in table 2. On POD 0, after discharge from the PACU, maximal and

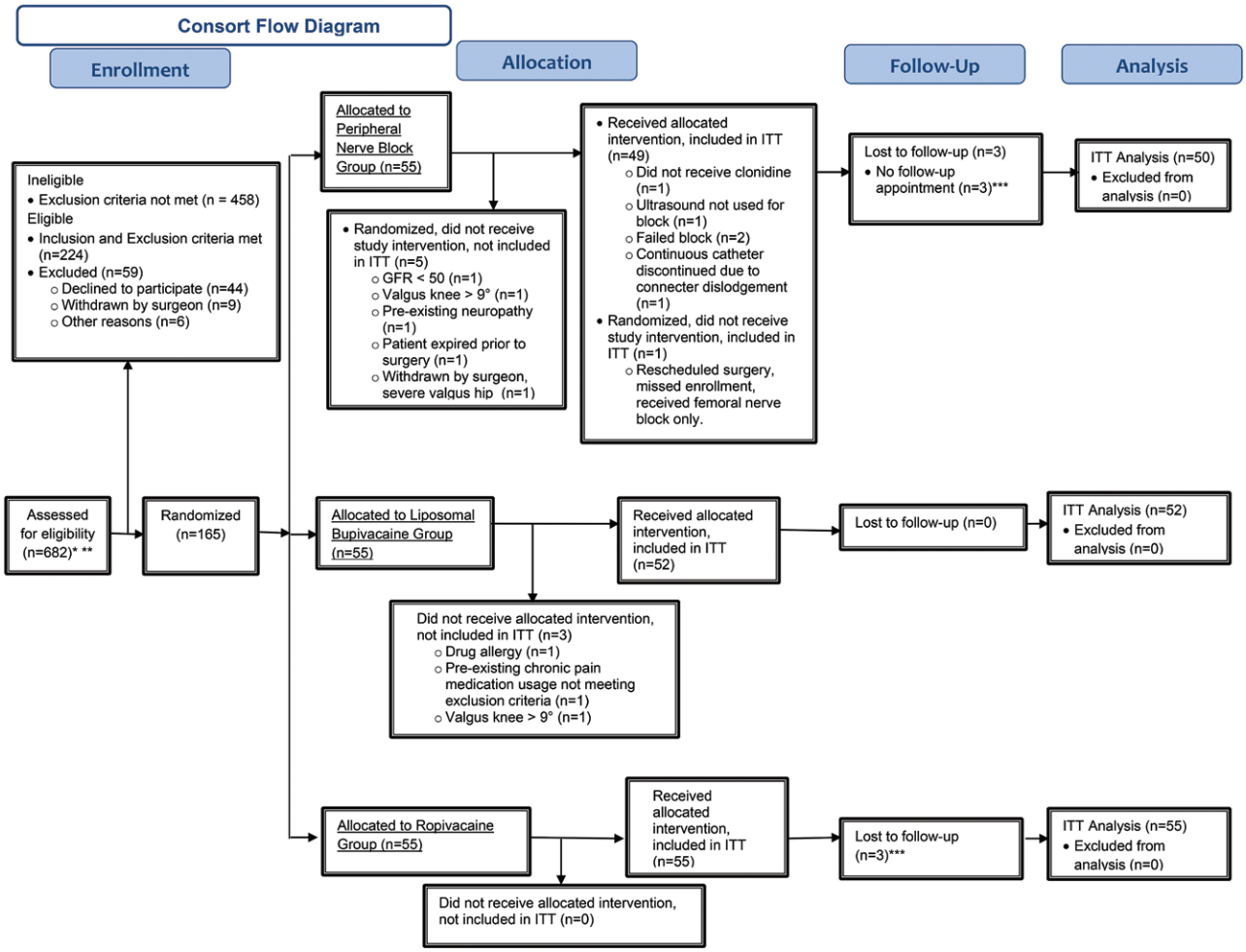

Fig. 3. Consort flow diagram. Study modifications: *exclusion criteria—body mass index threshold increased from 40 to 45 kg/m^2; **exclusion criteria—change in preexisting chronic opioid medication dose threshold; ***follow-up—addition of telephone follow-up encounter. GFR = glomerular filtration rate; ITT = intention to treat.

average pain scores were statistically significantly lower for the peripheral nerve block group compared to the ropivacaine periarticular injection group ($P < 0.001$, Hodges–Lehmann median difference [95% CI] = −2 [−3 to −1] for maximal pain; $P = 0.003$, −0.8 [−1.3 to −0.2] for average pain) and liposomal bupivacaine periarticular injection group ($P < 0.001$, −3 [−4 to −2] for maximal pain; $P < 0.001$, −1.4 [−2.0 to −0.8] for average pain). Our primary outcome measure of maximal pain measured on POD 1 6:00 AM to 12:00 PM showed a statistically significant difference with lower pain scores for patients in the peripheral nerve block group compared to the liposomal bupivacaine periarticular injection group (Hodges–Lehmann median difference [95% CI] = −1 [−2 to 0]; $P = 0.016$); however, no significant difference was seen between the peripheral nerve block and ropivacaine groups (−1 [−2 to 0]; $P = 0.144$) and the ropivacaine and liposomal bupivacaine groups (−0.5 [−1 to 0]; $P = 0.196$). Since baseline group differences were larger than expected, *post hoc* multivariable analyses were performed for the primary endpoint (maximal pain on POD 1, 6:00 AM to 12:00 PM) to assess differences between treatment groups after adjusting for sex, ASA status, and type of anesthesia. In all cases, the results from the adjusted analyses were similar to those obtained from the primary analysis (peripheral nerve block *vs.* ropivacaine periarticular: estimated mean difference [95% CI] = −0.4 [−1.4 to +0.6], $P = 0.454$; peripheral nerve block *vs.* liposomal bupivacaine periarticular: −1.1 [−2.0 to −0.1], $P = 0.033$; and ropivacaine periarticular *vs.* liposomal bupivacaine periarticular: −0.7 [−1.6 to +0.2], $P = 0.120$).

POD 1 average pain scores were significantly lower for the peripheral nerve block group *versus* the liposomal bupivacaine periarticular injection group (Hodges–Lehmann median difference [95% CI] = −1.0 [−1.7 to −0.3]; $P = 0.005$), but again differences were not statistically significant between the peripheral nerve block group and the ropivacaine periarticular injection group (−0.7 [−1.4

Table 1. Patient and Procedural Characteristics

Characteristics	PNB (n = 50)	Ropivacaine (PAI-R) (n = 55)	Liposomal Bupivacaine (PAI-L) (n = 52)
Age, yr	67 ± 9	68 ± 8	67 ± 8
Sex, n (%)			
Male	25 (50)	21 (38)	25 (48)
Female	25 (50)	34 (62)	27 (52)
Body mass index, kg/m^2	30.8 ± 6.0	30.3 ± 4.7	31.4 ± 5.6
ASA status, n (%)			
I/II	36 (72)	48 (87)	45 (87)
III	14 (28)	7 (13)	7 (13)
Type of anesthetic, n (%)			
General	14 (28)	8 (15)	14 (27)
Spinal	36 (72)	47 (85)	38 (73)
Duration of surgery, min	84 ± 18	87 ± 18	88 ± 24

ASA = American Society of Anesthesiologists; PAI-L = periarticular injection liposomal bupivacaine; PAI-R = periarticular injection ropivacaine; PNB, peripheral nerve block.

Table 2. Postoperative Pain*

Pain Assessment	PNB (n = 50†)	Ropivacaine (PAI-R) (n = 55†)	Liposomal Bupivacaine (PAI-L) (n = 52†)	Pairwise Comparisons‡		
				PNB *vs.* PAI-R Estimate (95% CI) *P* Value	PNB *vs.* PAI-L Estimate (95% CI) *P* Value	PAI-R *vs.* PAI-L Estimate (95% CI) *P* Value
Primary endpoints						
POD 1 (06:00–12:00) maximum pain	3 (1, 6)	4 (2, 6)	4.5 (3, 6)	−1 (−2 to 0) 0.144	−1 (−2 to 0) 0.016	−0.5 (−1 to 0) 0.196
Secondary endpoints						
POD 0, post-PACU						
Average	0.6 (0.0, 2.2)	1.7 (0.9, 2.5)	2.4 (1.1, 3.6)	−0.8 (−1.3 to −0.2) 0.003	−1.4 (−2.0 to −0.8) < 0.001	−0.6 (−1.1 to −0.1) 0.021
Maximum	1 (0, 4)	4 (2, 6)	5 (3, 6)	−2 (−3 to −1) < 0.001	−3 (−4 to −2) < 0.001	−0.5, (−1 to 0) 0.257
POD 1						
Average	2.5 (1.2, 4.2)	3.5 (2.5, 4.4)	3.7 (2.9, 4.6)	−0.7 (−1.4 to 0.0) 0.059	−1.0 (−1.7 to −0.3) 0.005	−0.3 (−0.9 to 0.2) 0.214
Maximum	5.5 (3, 7)	6 (5, 7)	6 (5, 8)	−1 (−2 to 0) 0.189	−1 (−2 to 0) 0.043	−0.5 (−1 to 0) 0.357
POD 2						
Average	3.3 (2.0, 4.2)	3.2 (2.4, 4.0)	3.5 (2.8, 4.3)	0.6 (−0.4 to 1.7) 0.958	−0.4 (−1.0 to 0.2) 0.203	−0.4 (−0.9 to 0.1) 0.132
Maximum	5 (3, 7)	6 (4, 7)	6 (5, 7)	0 (−1 to 1) 0.493	−1 (2 to 0) 0.299	0 (−1 to 1) 0.797

*Data are presented as median (25th, 75th). †For postoperative day 2, data are missing for five subjects (one peripheral nerve block, one periarticular injection ropivacaine, three periarticular injection liposomal bupivacaine). ‡Pairwise treatment comparisons were performed using nonparametric methods with results summarized by presenting the point estimate (95% CI) for Hodges–Lehmann median difference and the *P* value for the rank sum test.

PACU = postanesthesia care unit; PAI-L = periarticular injection liposomal bupivacaine; PAI-R = periarticular injection ropivacaine; PNB = peripheral nerve block; POD = postoperative day.

to +0.0]; $P = 0.059$) and the ropivacaine *versus* the liposomal bupivacaine periarticular injection groups (−0.3, [−0.9 to +0.2]; $P = 0.214$). On POD 2, no significant differences were detected in pain scores across all groups. The only time period in which the estimated median difference between groups represented a clinically significant difference (NRS pain score difference greater than or equal to 2) was maximal pain on POD 0 between the peripheral nerve block group and both periarticular injection groups.

Opioid consumption was less on POD 0 in the peripheral nerve block group compared to the periarticular injection groups (ropivacaine: $P = 0.012$, Hodges–Lehmann median difference [95% CI] = −4 [−8 to 0] mg oral morphine equivalents; liposomal bupivacaine: $P < 0.001$, −8 [−15 to 0] mg oral morphine equivalents; table 3). On POD 1, this reduction was only statistically significant for the peripheral nerve block group compared to the liposomal bupivacaine periarticular injection group ($P = 0.007$; −19 [−31 to −8] mg oral morphine equivalents). Consistent with differences in pain scores, the need for rescue intravenous opioid analgesics during the hospital stay was different across groups, with higher use of rescue analgesia in the liposomal bupivacaine periarticular injection group compared to the ropivacaine periarticular injection and peripheral nerve block groups ($P = 0.004$; liposomal bupivacaine group [n = 8]; ropivacaine group [n = 0]; peripheral nerve block group [n = 2]; table 4).

Additional hospital outcomes are summarized in tables 3 and 4; month outcomes are summarized in table 5. Overall, the frequency of adverse outcomes during the hospital stay and by 3 months postoperatively was low. Four patients fell during the study time period (3 months): two in the peripheral nerve block group fell during their hospital stay; and one in the ropivacaine periarticular injection group and one in the liposomal bupivacaine periarticular injection group fell after hospital discharge. Six patients, two in each group, experienced a superficial wound infection that required treatment with antibiotics. At 3-month follow-up, 36-Item Short-Form physical composite scores showed an improvement from baseline in all groups (table 5). The change from baseline to 3 months in unipedal stance time did not differ significantly across groups (group-by-time interaction, $P = 0.102$); however, the ropivacaine ($P = 0.001$) and liposomal bupivacaine ($P = 0.048$) periarticular injection groups showed an improvement from baseline while no evidence of improvement was seen for the peripheral nerve block group ($P = 0.623$).

Discussion

The combination of a femoral nerve catheter and single-injection sciatic block as part of a multimodal total joint pathway provides excellent, potentially complete analgesia after total knee arthroplasty.[33] Whether this is the ideal analgesic regimen remains a source of debate. This is the first randomized clinical trial that compares peripheral nerve blockade to two distinct periarticular injections, one with a ropivacaine mixture and the other with a liposomal bupivacaine mixture. All three analgesic modalities provided clinically satisfactory analgesia (average NRS < 4). The peripheral nerve block group had statistically significantly better average and maximal pain scores with less opioid use compared to the ropivacaine periarticular injection group in the immediate postoperative time period (POD 0). In addition, the peripheral nerve block group had statistically lower average pain scores than the liposomal bupivacaine periarticular injection group on POD 0 and 1, while no statistical differences were seen when comparing the two periarticular

Table 3. Opioid Use*

Pain Assessment	PNB (n = 50†)	Ropivacaine (PAI-R) (n = 55†)	Liposomal Bupivacaine (PAI-L) (n = 52†)	Pairwise Comparisons‡: PNB *vs.* PAI-R Estimate (95% CI) *P* Value	Pairwise Comparisons‡: PNB *vs.* PAI-L Estimate (95% CI) *P* Value	Pairwise Comparisons‡: PAI-R *vs.* PAI-L Estimate (95% CI) *P* Value
Preoperative, mg OME	15 (0, 15)	15 (0, 15)	15 (0, 15)	0 (0 to 0) 0.571	0 (0 to 0) 0.991	0 [0 to 0] 0.496
Intraoperative, mg OME	10 (5, 15)	10 (5, 15)	10 (7, 20)	1 (0 to 3) 0.807	−3 (−5 to 0) 0.171	−3 (−5 to 0) 0.104
PACU, mg OME	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0 to 0) 0.454	0 (0 to 0) 0.475	0 (0 to 0) 0.134
POD 0 post-PACU, mg OME	0 (0, 15)	8 (0, 30)	15 (0, 30)	−4 (−8 to 0) 0.012	−8 (−15 to 0) < 0.001	−4 (−8 to 0) 0.293
POD 1, mg OME	26 (0, 53)	38 (15, 53)	45 (15, 82)	−11 (−23 to 0) 0.202	−19 (−31 to −8) 0.007	−14 (−30 to 2) 0.148
POD 2, mg OME	23 (0, 38)	15 (0, 38)	23 (15, 45)	0 (−8 to 8) 0.933	−8 (−15 to 0) 0.169	−8 (−15 to 0) 0.126

*Data are presented as median (25th, 75th). †For POD 2, data are missing for five subjects (one PNB, one periarticular injection ropivacaine, three periarticular injection liposomal bupivacaine). ‡Pairwise treatment comparisons were performed using nonparametric methods with results summarized by presenting the point estimate (95% CI) for Hodges–Lehmann median difference and the *P* value for the rank sum test.

OME = oral morphine equivalents; PACU = postanesthesia care unit; PAI-L = periarticular injection liposomal bupivacaine; PAI-R = periarticular injection ropivacaine; PNB, peripheral nerve block; POD = postoperative day.

Table 4. Hospital Outcomes*

Characteristics	PNB (n = 50)	Ropivacaine (PAI-R) (n = 55)	Liposomal Bupivacaine (PAI-L) (n = 52)	*P* Value*
Hospital LOS, days	2 (2, 3)	2 (2, 3)	2 (2, 3)	0.768
Any rescue IV opioid	2 (4)	0 (0)	8 (15)	0.004
Any adverse events	2 (4)	1 (2)	1 (2)	0.732
Fall	2	0	0	
Nerve injury	0	0	0	
Infection	0	0	0	
ICU admission	0	0	0	
Rapid response team	0	1	1	
Additional surgery	1	0	0	
Death	0	0	0	

*Hospital LOS is presented as median (25th, 75th) and compared across groups using the Kruskal–Wallis test. Other outcomes are compared across groups using Fisher exact test.

ICU = intensive care unit; IV = intravenous; LOS = length of stay; PAI-L = periarticular injection liposomal bupivacaine; PAI-R = periarticular injection ropivacaine; PNB = peripheral nerve block.

Table 5. Three Month Outcomes

Characteristics	PNB (n = *)	Ropivacaine (PAI-R) (n = *)	Liposomal Bupivacaine (PAI-L) (n = *)	*P* Value†
SF-36 Physical Composite Scale				
Baseline	31.6 ± 8.2	30.5 ± 8.0	33.6 ± 8.1	0.169
Follow-up	39.2 ± 9.9	42.0 ± 9.9	42.5 ± 9.8	0.218
Delta	7.6 ± 10.9	11.4 ± 10.2	9.0 ± 11.6	0.211
P value (baseline vs. 3 months)	< 0.001	< 0.001	< 0.001	
SF-36 Mental Composite Scale				
Baseline	56.8 ± 7.9	59.7 ± 7.2	53.8 ± 10.5	0.004
Follow-up	59.6 ± 4.5	57.2 ± 6.3	55.9 ± 8.0	0.022
Delta	2.8 ± 8.0	–2.5 ± 8.0	2.1 ± 8.6	0.003
P value (baseline vs. 3 months)	0.022	0.031	0.087	
Unipedal stance (operative leg), s				
Baseline	24 (7, 30+)	16 (5, 30+)	17 (3, 30+)	0.632
Follow-up	20 (8, 30+)	30+ (11, 30+)	23 (8, 30+)	0.370
P value (baseline vs. 3 months)	0.623	0.001	0.048	0.102
NRS pain score, 0–10				
Pain at rest				
Median (25th, 75th)	0 (0, 2)	1 (0, 2)	1 (0, 2)	0.811
>3, n (%)	5 (29)	6 (35)	6 (35)	1.00
Pain with movement				
Median (25th, 75th)	2 (1, 3)	2 (0, 3)	1.5 (0, 3)	0.302
>3, n (%)	10 (34)	11 (38)	8 (28)	0.782
Problems since surgery, n (%)				
Nerve injury	2 (4)	0 (0)	0 (0)	0.096
Infection	2 (4)	2 (4)	2 (4)	1.00
Fall requiring medical attention	0 (0)	1 (2)	1 (2)	1.00

*For SF-36 composite scales, n = 46, 51, and 49 for regional, ropivacaine, and liposomal bupivacaine, respectively; for unipedal stance n = 45, 49, and 50; for pain and problems since surgery n = 46, 51, and 50. †SF-36 composite scales are summarized using mean ± SD, with within-group comparisons of baseline and 3 months performed using the paired Student's *t* test and between-group comparisons performed using analysis of variance. Unipedal stance data are summarized using median (25th, 75th), with within-group and between-group comparisons performed using proportional hazards regression to take into account the censored data with random effects used to accommodate repeated measurements within subjects at baseline and 3 months. Pain scores at 3 months are compared across groups using the Kruskal–Wallis test. The percentage of patients with pain greater than 3 and the percentage of patients reporting problems since surgery are compared across groups using Fisher exact test.

NRS = numeric rating scale; PAI-L = periarticular injection liposomal bupivacaine; PAI-R = periarticular injection ropivacaine; PNB = peripheral nerve block; SF-36 = Medical Outcomes Study 36-Item Short-Form.

injection solutions (ropivacaine and liposomal bupivacaine). Despite the statistical differences in pain scores that were detected in this study, these findings may not be clinically meaningful as an estimated median difference in NRS pain score of greater than 2 was only observed for maximal pain at one time point (POD 0) favoring the peripheral nerve block group more than the ropivacaine periarticular injection and liposomal bupivacaine periarticular injection groups.

However, based on the CIs presented in table 2, our findings also cannot exclude the possibility that a difference of 2 could exist between the peripheral nerve block and the two periarticular injection groups at other time points.

Our study was unable to demonstrate the superiority of a periarticular injection using a liposomal bupivacaine-based local anesthetic solution over a ropivacaine-based solution for total knee arthroplasty. This finding is consistent with other recent studies showing no additional benefit of liposomal bupivacaine use compared to nonliposomal forms of local anesthetics in periarticular injection for total knee arthroplasty.[21] Our results included consistently higher NRS pain scores and opioid consumption in the liposomal bupivacaine periarticular injection group compared to the ropivacaine periarticular injection group throughout hospitalization. The need for rescue intravenous analgesia was also different across treatment groups, with the results favoring the ropivacaine periarticular injection group; a total of 10 patients in our study required intravenous opioid rescue pain medications for relief of severe pain during their stay. Eight of these 10 patients who received rescue intravenous analgesia were in the periarticular injection liposomal group, while zero patients in the ropivacaine group required intravenous rescue.

This study was unique in its ability to collect intermediate functional outcomes (unipedal stance time, 36-Item Short-Form) and chronic pain. Health-related quality of life was assessed through the Medical Outcomes Study 36-Item Short-Form questionnaire at 3 months, and all groups improved from baseline in the physical composite scale. Chronic pain was evaluated at 3 months postoperatively, and patients were asked to complete the LANSS. One patient in the peripheral nerve block group scored positive for the LANSS criteria indicative of neuropathic pain; however, this finding is inconsistent with the medical record as the patient reported a pain score of 2 out of 10 to the surgeon at the same time interval and demonstrated a normal physical and sensory exam of the operative extremity. Furthermore, two patients in the peripheral nerve block group responded in the affirmative to nerve injury at 3 months. In both patients, the nerve injury was described as bilateral tingling in their feet and unlikely related to the study intervention. One patient was subsequently diagnosed with spinal stenosis, and the other likely suffered from progression of poorly controlled diabetes.

Unipedal stance time threshold of 30 s was collected to help identify a patient with a higher risk for falling.[34] There were no statistically significant differences in the balance measurement between the three groups at 3 months, likely reflecting the high baseline balance ability in patients across the groups; however, this study was not powered to detect a difference. We did observe that patients in the periarticular injection groups demonstrated an improvement in unipedal stance times from baseline. It is yet to be determined whether unipedal stance time is able to show promise as an intermediate functional outcome measure or if an alternative measure is more predictive for fall risk after total knee arthroplasty. The importance of predicting patients at high risk for falling and the implementation of additional measures to prevent falls after total knee arthroplasty cannot be overstated. Within the study surveillance period (3 months), four falls were observed (two inpatient and two out of hospital). The two inpatient falls (both in the peripheral nerve block group) resulted in an overall in-hospital fall incidence of 1.29% (2 of 155), which is consistent with the expected fall rate for hospitalized patients undergoing a total knee arthroplasty with peripheral nerve blockade (1.62 to 7%) and not outside the expected rate for falling after total knee arthroplasty with and without the influence of peripheral nerve blockade (1.6%).[13,35] Unfortunately, both of the patients who fell required reoperation (a marker for serious injurious falls). Not unlike previous studies on fall risk after total knee arthroplasty,[36,37] the inpatient falls in the peripheral nerve block group occurred during the intermediate phase (on or after POD 2) of their recovery and after removal of the peripheral nerve catheter. Fall precautions were in place and in both instances the patient disregarded nursing instructions and tried to ambulate without assistance or aid. Since the falls in our study occurred after removal of femoral nerve block, we continue to emphasize that there should be strict adherence to fall-prevention strategies during the entire hospitalization and after dismissal regardless of regional anesthetic technique. Two additional patients fell at home, one in the liposomal bupivacaine periarticular injection group and one in the ropivacaine periarticular injection group, with one fall causing wound dehiscence, which did not require reoperation.

As this was a randomized study reflecting current practice trends of periarticular injections for total knee arthroplasty conducted at a high-volume, large academic orthopedic center, this study has several strengths. This study was sufficiently powered to detect not only a difference in the primary outcome but also NRS pain scores and opioid consumption at other time periods as well.

The anesthesiologists have a primary focus in regional anesthesia for orthopedic surgery, and the surgeons all have consistent and uniform surgical and periarticular injection techniques. We have worked collaboratively during the past 14 yr to develop, evaluate, and revise a comprehensive multimodal analgesic pathway for patients undergoing total knee arthroplasty. This study was undertaken to help determine the best analgesic pathway for these patients.

The main limitation of the current study was an inability to mask participants and providers to the comparison between peripheral nerve blockade and periarticular injection within our multimodal clinical pathway. This unmasking may introduce some risk of bias from patients and providers. However, masking was possible between the two periarticular

injection groups, and outcome assessment by adjudicators and all statistical analyses were conducted in a blinded fashion. In addition, although patients were randomized, baseline group differences were larger than expected (example: the ropivacaine group received a higher number of spinal anesthetics compared to the liposomal bupivacaine and peripheral nerve block groups; $P = 0.18$); however, our findings remained relatively unchanged from *post hoc* analyses of the primary endpoint, which adjusted for these baseline imbalances. Therefore, larger studies may allow for a better balance of baseline covariates to confirm these results.

The study design allows for generalizability and real-world assessment of the perioperative management of total knee arthroplasty. One of the biggest advantages of periarticular injections at our institution is the lack of need for vascular access in the postoperative period. It is our institutional policy to require intravenous access for patients with a peripheral nerve catheter in place in order to have access in the case of a need to treat local anesthetic toxicity. In this sense, periarticular injections allow for less medical intervention including freedom from continuous infusion pumps or invasive tubing that restricts mobility. Furthermore, periarticular injections may be associated with less nerve injury, motor weakness, nerve catheter dislodgement, and decreased workload.[6,8,13,19]

In summary, this study demonstrated that a multimodal analgesic pathway including periarticular injections with ropivacaine for total knee arthroplasty provides perioperative pain control that is comparable on POD 1 and 2 to a femoral nerve catheter and single-injection sciatic nerve block. We did not establish an advantage of liposomal bupivacaine over ropivacaine in periarticular injections for total knee arthroplasty. This study does not address the challenging, opioid-tolerant patient, nor did we address patient request or expectations of total knee arthroplasty perioperative pain management (*i.e.*, best analgesia *vs.* avoidance of additional invasive interventions). These are all factors that may influence the perioperative pain management for each individual patient. Our collective knowledge of the ideal analgesic modality might be improved by future studies that evaluate different peripheral nerve blockade techniques in combination with periarticular injections as recent evidence suggests that periarticular injections in conjunction with a peripheral nerve block provides better pain relief than periarticular injections alone.[17,31,38]

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Competing Interests

Dr. Taunton serves as a consultant at DJO Global (Vista, California). He receives royalties from DJO Global (Parsippany, New Jersey). Dr. Pagnano serves as a consultant at Pacira Pharmaceuticals. He receives the following royalties: DePuy intellectual property (IP) royalties, Johnson & Johnson IP royalties, Stryker IP royalties.

Reproducible Science

Full protocol available at: Amundson.Adam@mayo.edu. Raw data available at: Amundson.Adam@mayo.edu.

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